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DOI:

[10.1111/jan.13476](https://doi.org/10.1111/jan.13476)

Document Version

Peer reviewed version

[Link to publication record in King's Research Portal](#)

Citation for published version (APA):

Mansell, R., & Purssell, E. (2017). Treatment abandonment in children with cancer in Sub-Saharan Africa: systematic literature review and meta-analysis. *Journal of Advanced Nursing*. <https://doi.org/10.1111/jan.13476>

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Treatment abandonment in children with cancer in Sub-Saharan Africa: systematic literature review and meta-analysis.

Running head: Cancer treatment abandonment in Africa

Rikka MANSELL BSc

Student (BSc with RN Child)

Edward PURSSELL RGN RSCN PhD

Senior Lecturer

King's College London

James Clerk Maxwell Building

57 Waterloo Road

London SE1 8WA

Telephone: 020 7848 3021

Email: edward.pursell@kcl.ac.uk

No conflict of interest has been declared by the authors

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors

Treatment abandonment in children with cancer in Sub-Saharan Africa: systematic literature review and meta-analysis

Aims

To establish and quantify the main reasons for treatment abandonment in children with cancer in Sub-Saharan Africa through a systematic review of the literature.

Background

Great advances have been made in the treatment of childhood cancer, however this requires that families are able to complete treatment. Failure to do this is referred to as treatment abandonment, which is recognised as a reason for treatment failure.

Design

Systematic review and meta-analysis of data on the reasons for treatment abandonment in Sub-Saharan Africa.

Data sources

Ovid MEDLINE 1946 to May Week 1 2017 and Embase 1974 to 2017 Week 19. Additional hand-searching was undertaken.

Review methods

Two reviewers independently screened papers and extracted the data. The R package meta was used to calculate the relative risk of treatment abandonment or the proportion of parents stating a reason.

Results

The relative risk of treatment abandonment was highest for not being in a research cohort; followed by mothers only having primary education, being HIV negative, parents not being employed, travel, and no insurance. When parents who had abandoned treatment were asked, the most common reason was finance, followed by insurance, transport, lack of social support, their child appearing well, fear, and waiting.

Conclusions

More data are needed on the extent of treatment abandonment in different countries. Clinicians should encourage parents without insurance to enrol onto the relevant insurance programme straight after diagnosis, provide housing for patients and families close to the treatment centres, and to develop treatment at more localised centres.

Keywords: Cancer, Child health, Child Nursing, Oncology, Paediatric, Treatment Abandonment, Systematic Review.

Summary statement

Why is this research or review needed?

- It is estimated that 84% of all paediatric cancers cases worldwide occur in low to middle income countries where the survival rates can be as low as 10%, opposed to the high rates of survival 80%+ found in high income countries.
- Although there are many factors contributing to the discrepancy between survival rates, recent studies have reported treatment abandonment being as being a primary causes of therapeutic failure and death in paediatric cancer patients from resource poor countries, but the reasons for this vary between studies.

What are the key findings?

- Treatment abandonment is a significant problem in Sub-Saharan Africa, attributing to the low survival rates of paediatric cancer.
- Six factors were found in the literature that were clinically significant, associated with a high risk of treatment abandonment in Sub-Saharan Africa, these being: not being in a research cohort; mother being educated below secondary school level; the child being HIV negative; parental unemployment; travel and no access to hospital insurance.

How should the findings be used to influence policy/practice/research/education?

- Treatment abandonment is a major factor impeding progress in the treatment of cancer in children in developing countries, strategies should be developed to address the reasons found for this.
- Although essential, reducing treatment abandonment is one of six proposed strategies to improve care and outcomes for paediatric cancer patients in sub-Saharan Africa.

- Based on this review future research should focus on how children can be maintained on treatment as part of an overall measure of treatment efficacy.

Treatment abandonment in children with cancer in Sub-Saharan Africa: systematic literature review and meta-analysis

INTRODUCTION

Childhood cancer in developing countries is increasingly recognised as a matter of importance, with around 84% of childhood cancers occurring in low-middle income countries (LIC) in which 90% of the world's children live (Magrath et al., 2013). In Africa it is estimated that in 2012 there were 846 961 cases of cancer of which 36 428 were in children under the age of 15 years, with a total mortality of 591 169 and 21 341 respectively, while in sub-Saharan Africa it is estimated that there were 28 872 cases and 16 343 deaths in children (Ferlay et al., 2014).

In higher income countries (HIC) the advances in cancer treatment has been impressive. For example, for children diagnosed with cancer in the UK in 1990 the 10-year survival was 63.7%, while the equivalent figure for children diagnosed in 2015 is predicted to be 82.4% (ONS 2017); however similar successes have not been universally seen in less developed countries. Data on cancer in many parts of the world are limited by the lack of diagnostic facilities and high quality population-based cancer registries (Gelband et al., 2015), and even where individual hospitals keep records the loss to follow-up makes these unreliable. It was estimated in 2012 that fewer than 20% of children in Africa had access to curative treatment (Hadley et al., 2012), however even if treatments are available children may not be in a position to complete the necessary regimen, a phenomenon known as treatment abandonment.

Background

The term treatment abandonment is defined as the unsuccessful attempt to either begin or complete cancer treatment (Friedrich et al., 2015). As treatment abandonment encompasses the inability to start treatment as well as to continue it, its extent is unknown, however it is increasingly recognized as one of the primary causes of therapeutic failure and death in paediatric cancer patients from resource poor countries (Arora et al., 2007; Mostert et al., 2011; Gupta et al., 2013). In 2010 the International Society of Pediatric Oncology established the Abandonment of Treatment Working Group which made five recommendations: that abandonment of treatment be documented as an adverse event in childhood cancer studies in resource-poor countries; that abandonment of treatment be defined as failure either to begin (conventionally termed refusal) or to continue the planned course (abandonment); that abandonment of treatment be defined as a hiatus of 4 or more weeks in the scheduled treatment; that abandonment of treatment should be used only in the context of treatment given with the intention of cure; acknowledging that abandonment of treatment is as much a socioeconomic issue as a medical one, and is often the result of various factors beyond the control of the patients and parents (Mostert et al., 2011).

A global study of treatment abandonment suggested that around 15% (23 854 of 155,088 children <15 years old newly diagnosed with cancer) abandon treatment, with abandonment rates of 6% or more being reported in 9% of high income, 41% upper-middle, 80% lower middle, and 90% low income countries. Predictors of this were lower national income category, higher reliance on out-of-pocket payments, and high prevalence of economic hardship at the treatment centre (Friedrich et al., 2015). Although there are data regarding the reasons for treatment abandonment in individual or small groups of centres, there have so far been few attempts to quantify this phenomenon on a regional basis, which may hinder

effective action, particularly in the absence of robust local health systems. This review seeks to assist in this process by reviewing the reasons for treatment abandonment in one defined region which has a unique set of circumstances, that of Sub-Saharan Africa.

THE REVIEW

Aim

This study aims to establish and quantify the main reasons for treatment abandonment in children with cancer in Sub-Saharan Africa through a systematic search and review of the literature.

Design

This review was conducted according to the methods contained within the Cochrane Manual 5. 1 (Higgins & Green, 2011) and the PRISMA reporting guidance (Moher et al., (2009), with quantitative analyses being done using the meta package (Schwarzer, 2017) in R (R Core Team, 2017). There is no published protocol for this, but full details of the review and analysis are in the supplementary material.

Search methods

The eligibility criteria for the review was that studies had to be conducted on children or young people under the age of 18 years in sub-Saharan Africa; and to provide data on the number of children diagnosed with cancer, and the number who abandoned treatment sufficient to allow calculation of a proportion or relative risk for the reasons for abandonment. Two databases were searched, Ovid MEDLINE 1946 to May Week 1 2017 and Embase 1974 to 2017 Week 19; the full search strategy is shown in the supplementary material. Briefly the population of interest were children with any diagnosis of cancer or

malignancy in sub-Saharan Africa, and the outcome was treatment abandonment, compliance or adherence. Additional hand-searching was undertaken using Google and reference lists of papers.

Two reviewers independently screened papers for compliance with the inclusion criteria and extracted the data, which consisted of the total number of children in the cohort and the number and reason for abandoning treatment. These were entered into a spreadsheet and subsequently the R package meta was used to calculate the relative risk of treatment abandonment or the proportion of parents stating a reason for this (R Core Team, 2017; Schwarzer, 2017). The summary forest plots were drawn in the forestplot package (Gordon & Lumley, 2017). Where there was more than one study reporting an outcome meta-analysis was undertaken, however due to the small number of studies the resulting heterogeneity statistics need to be interpreted with caution. The risk of bias was assessed using the Newcastle Ottawa Scale (Wells et al., 2014). This tool is used to assess the quality of non-randomized studies across three broad areas: selection, which includes representativeness of the groups, ensuring they have the exposure of interest and that the outcome was not present before the exposure; comparability with regards to possible confounders; and outcome, how the outcome was assessed and if sufficient time was given for it to occur.

Search outcome

The search resulted in 64 studies after duplicates were removed; a further 50 were not relevant due to not being primary research or in the wrong population. Of the remaining 14 papers, 6 were not conducted in Sub-Saharan Africa or had no extractable data, and one was about the retention of children in hospital when their relatives were not able to pay bills rather than abandonment. Six papers were included in the final analysis, full details of study

selection is shown in Figure 1. Eight studies were excluded; a full list of these and the reasons for exclusion are shown in the supplementary material. All studies were cohort studies, four were single centre (Mostert et al., 2014; Mtete et al., 2016; Njuguna et al., 2014; Sloane et al., 2014) and two multi-centre (Axt et al., 2013; Libes et al., 2015). The countries in which the studies took place were Kenya (Axt et al., 2013; Libes et al., 2015; Mostert et al., 2014; Njuguna et al., 2014), Malawi (Mtete et al., 2016) and Zambia (Sloane et al., 2014).

Quality appraisal

The risk of bias in each study was assessed using the Newcastle-Ottawa Scale, the summary of the findings are shown in Table 1. Briefly all studies scored highly for selection apart from one where the comparison cohort had different forms of cancer (Mtete et al., 2016); for comparability two studies had no comparison group at all meaning only proportions could be calculated (Libes et al., 2015, Njuguna et al., 2014); and all studies had large loss of subjects of unknown significance. Two studies also used self-report measures (Libes et al., 2015, Njuguna et al., 2014), although as this subject has high saliency and this is an appropriate way of collecting these data, no reduction was made for this.

Data abstraction and synthesis

Six studies were included in the final analysis, of these: three were retrospective reviews of children treated for Wilm's tumour in Kenya (Axt et al., 2013) and various forms of cancer in Kenya (Mostert et al., 2014) and Zambia (Sloane et al., 2014); two were based on interviews with parents of children who had abandoned care in Kenya (Libes et al., 2015, Njuguna et al., 2014), and one compared a retrospective general cancer group with prospective Kaposi's sarcoma and Burkett's lymphoma groups in Malawi (Mtete et al., 2016). For the two studies based on interviews with parents no comparison group existed, so only the proportions who

attributed abandonment of treatment to different factors could be calculated; for other studies the risk and relative risk of having the characteristic among those who did and did not abandon treatment was able to be calculated.

Two types of data were extracted from the papers, those that allowed the risk and relative risk of abandonment associated with particular characteristics to be calculated; and those for which only the proportion of those citing a reason for abandoning treatment was given. Data were extracted by the two authors independently using a common data extraction tool to identify key demographic and methodological features as well as numeric outcome data. No significant differences occurred between authors. These results are shown in Figure 2 and Figure 3. For insurance and maternal education where there was more than one study reporting these data meta-analysis of relative risks was done, and for appeared well and finance a meta-analysis of proportions was conducted.

RESULTS

The relative risk for treatment abandonment was calculated for six characteristics, most of which are based on single studies apart from education and insurance for which pooled estimates are given. The RRs were 3.67 (1.34 to 10.05) for not being in a research cohort; 2.27 (95% CI 1.53 to 3.36), $Q=0.59$, $df=1$, $p=0.4417$, $I^2=0\%$ for only having primary education; 2.10 (0.88 to 5.02) for being HIV negative; 1.72 (0.91 to 3.76) for parents not being employed; 1.51 (0.83 to 2.74) for travel, and 1.29 (0.98 to 1.71), $Q=1.41$, $df=1$, $p=0.2351$, $I^2=29.1\%$ for not having insurance.

For those studies asking parents who had abandoned treatment why they had done so, 56% gave no reason (38 to 73); this was followed by finance 32% (15 to 71), $Q=4.27$, $df=1$, $p=0.0387$, $I^2=76.6\%$; insurance 27% (12 to 48); transport 23% (9 to 44); lack of social support

12% (2 to 30); appeared well 10% (3 to 33), $Q=1.67$, $df=1$, $p=0.1956$, $I^2=40.3\%$; fear 9% (2 to 24) and waiting by 3% (0 to 15). As with the relative risks most of these are based on single studies except finance and their child appearing well.

DISCUSSION

A general review of strategies to improve care for children with cancer in sub-Saharan Africa listed six challenges for improving outcomes: reducing late presentation and underdiagnosis; reducing malnutrition; adjusting treatment intensity to local circumstances; better supportive care; improving diagnosis and evaluation of treatment outcomes, and reducing treatment abandonment (Israels et al., 2010). However, in order to reduce treatment abandonment the factors contributing to this phenomenon must first be identified. Our review identified six factors in the literature that were particularly associated with a high risk of treatment abandonment in Sub-Saharan Africa, these being: not being in a research cohort; mother being educated below secondary school level; the child being HIV negative; parental unemployment; travel and no access to hospital insurance. Although only the first two of these were statistically significant, others of these may still have clinical significance, with the lack of statistical significance being due to wide confidence intervals resulting from relatively small sample sizes.

The factor associated with the greatest increase in treatment abandonment was not being involved in research, although in the one study that looked at this, a general cancer cohort ($n=240$) was compared with much smaller Kaposi sarcoma ($n=25$) and Burkitt lymphoma ($n=73$) research groups introducing a high degree of indirectness for the aim of this review. Although being in the general (non-researched) group did increase the risk of treatment abandonment by 267%, there are numerous other possible factors here such as the nature of

the treatments, which are very different, although it is also plausible that more efforts are made by researchers and clinicians to retain children in research projects than those who are not.

Maternal education to less than secondary school level resulted in a 127% increase in treatment abandonment. Only two studies were entered into the meta-analysis making the heterogeneity statistic unreliable, but the results were similar between the two studies. There is also some resonance between this and the finding that those around the family, both in hospital and the community can have major influences on parental decision making, and if the parents have insufficient education to contextualise arguments such as “the life of your child is in God’s hands” which was a topic discussed with other parents on the ward by 27 of 31 (87%) of parents in one study of families who abandoned treatment, it is easy to see how this could negatively impact on decision making (Mostert et al., 2014).

However, low education does not occur in isolation, and these and other studies have reported that reasons for treatment abandonment in low income countries regularly incorporate both educational and financial deficits (Arora et al., 2007; Mostert et al., 2010; Sitaresmi et al., 2010). In Indonesia, a parental education programme was introduced for patients with acute lymphoblastic lymphoma (ALL) with the aim of providing readily accessible information about the disease and benefits of treatment, this resulted in a decrease in treatment abandonment from 14% to 2% (Mostert et al., 2010). Healthcare professionals can also help to decrease problems faced by parents lacking education by providing the correct information regarding the disease, treatment options, and help to settle cultural beliefs that cancer is not curable (Njuguna et al., 2014).

The risk associated with the child's HIV status and parental unemployment were similar, although only one study provided data including patient characteristics for both HIV positive and negative diagnosis and whether these individuals abandoned treatment or not (Sloane et al., 2014). This information was available because the study reported that the Department of Paediatrics and Child Health at the University Teaching Hospital in Zambia where the study was carried out implemented a routine opt out HIV testing for every child admitted from 2005 (Slone et al., 2014). The reasons for the lower risk attached to being HIV positive was not investigated in this study; however it may be that being more aware of their child's medical fragility parents were more highly motivated to continue treatment, or that they had access to cancer treatments through HIV-related services.

Parental unemployment leading to financial difficulties has been reported in a number of studies as a significant cause of treatment abandonment in LIC including those in sub-Saharan Africa (Arora et al., 2010; Kumar et al., 2013; Njuguna et al., 2014; Naderi et al., 2016). Although the meta-analysis performed during this review did not find parental unemployment as the most significant risk factor of treatment abandonment, the RR showed a 72% increased risk of treatment abandonment associated with parental unemployment. One study reported that in 60% of the families treatment abandonment occurred later than 3 months post diagnosis (Njuguna et al., 2014), which is uncommon as treatment abandonment usually occurs within the first few weeks of diagnosis (Arora et al., 2010; Gupta et al., 2013; Kumar et al., 2013.) It was suggested that this finding was related to Kenyan hospital retention policies by which patients are held in hospital until their bill is paid (Mostert et al., 2014). This implies that most patients receive medical treatment originally, and continue until the family are presented with a large hospital bill that they cannot afford, resulting in treatment abandonment (Mostert et al., 2014). Of the families included in this study, 74%

reported having to sell whatever was accessible to them including land and livestock in order to help with their financial difficulties related to starting treatment for their child, and 52% of families ended up in such severe debt, that they are still making payments up to 5 years after treatment started (Njuguna et al., 2014). For most families, treatment is simply unaffordable, and the sick child becomes a considerable financial burden on the family (Mostert et al., 2014).

Travel was identified as increasing the risk of treatment abandonment by around 50%. It was mentioned as the third most common reason in one study (Njuguna et al., 2014) and as a reason by 52% in another (Sloane et al., 2014). Whilst distance to the nearest treatment centre is the main factor related to treatment abandonment, travel encompasses a variety of factors including quality of roads, amount of time spent travelling between home and the treatment centre, and availability of transport to travel to the desired destination.

Due to limited resources in Sub-Saharan Africa, many families live a great distance from the nearest treatment centre. Although distances vary in these studies some of the distances travelled were great, for example in one study two-thirds of the patients resided over 300km away from the treatment centre (Slone et al., 2014). Public transport in Kenya, which was the means of travel to the treatment centre for 46% of the patients in one study (Njuguna et al., 2014) is relatively unorganised and unreliable with no specified timetable, routes that can be changed midway throughout a journey, and unexpected price increases (Njuguna et al., 2014). This can make it very difficult for families having to travel regularly to the treatment centre, as this can increase the financial strains these families are already subject to, and can also cause job insecurity as having to take time off could result in job unemployment further increasing the risk of treatment abandonment. This was also reported during a study in

Malawi during family interviews where it was reported that there was a large concern over absence from home during treatment and increased expenses related to travel to and from the treatment centre (Israels et al., 2008). Distance to the treatment centre can impact on delayed presentation to seek medical attention, enhancing the risk of treatment abandonment. This was demonstrated by the fact that the mean duration of symptoms prior to diagnosis was longest in children living furthest from the treatment centre, and these children were more likely to abandon treatment (Slone et al., 2014).

Both studies suggested in order to help extinguish travel as a predictive factor of treatment abandonment and attempt to increase paediatric cancer outcomes, there should be some form of accommodation provided for children and their families nearer the treatment centre to help alleviate time and cost spent on travel. These suggestions are based on research carried out in Brazil for patients diagnosed with ALL, which found that by providing accommodation, food, and assistance with transportation, treatment abandonment was almost eradicated during a 20-year period (Howard et al., 2004). Another suggestion was providing treatment in regional centres closer to where the patients are living, although with very limited resources already the first suggestion may be a more realistic option to help reduce treatment abandonment and aim to increase paediatric cancer survival.

The final factor identified was access to health insurance. Although the costs of the Kenyan National Hospital Insurance Fund (NHIF) are reported to be generally affordable for Kenyans, even those living under the poverty line; only 34 patients out of 148 had NHIF (Mostert et al., 2014). No access to NHIF increased the risk of treatment abandonment by 29% therefore it is essential for healthcare professionals to inform parents about the option of acquiring NHIF at diagnosis. Some parents involved in the study were only informed of

access to NHIF up to two and half months after diagnosis, by which point the financial burden had already caused parents to abandon treatment (Mostert et al., 2014). One hospital in Kenya has recently enforced that all newly diagnosed cancer patients apply for enrolment into the NHIF to help ensure that children have access to NHIF in hopes that it will decrease treatment abandonment, as enrolment into the NHIF is associated with an increased chance of treatment completion. Parents reported that the application process for NHIF was complex, and there was a period of up to 3 months before insurance was provided to cover hospital bills after the application was completed (Njuguna et al., 2014). As there is increased risk of treatment abandonment with no access to health insurance, governments should ensure more families are enrolled in a health insurance programme, by simplifying the application process and informing parents in depth to the advantages of enrolling. Interestingly both Mostert et al (2014) and Axt et al (2014) noted that although there was data provided as to whether individuals had NHIF or not, there was no information surrounding the patients socio-economic status. Access to NHIF therefore could be a proxy marker of families in a higher-socioeconomic status, who would have the ability to pay further medical costs, resulting in improved outcomes and decreasing the risk of treatment abandonment.

Many of these factors concur with what parents themselves report as reasons for abandoning treatment, two studies having a pooled percentage of 32% mentioning this, where 27% mention insurance, 23% transport, 12% social support, 10% that their child appeared well, and 9% fear. However, the fact that parental report is different in some respects to those gleaned from records alone, emphasises the importance of asking parents about their views as well as using records. Hospital based records and registries record what is deemed important by healthcare professionals rather than parents and families, and often what is easy to record.

The issue of social support may be more important than the quantitative analysis of records suggests. A study involving parents of children who had abandoned treatment in Kenya showed how important family members, the local community, church leaders and parents of other children in hospital can be in influencing parental decision making; with recommendations to stop or seek alternative treatments being common from members of their home community, and their child's life being in God's hands or cancer being untreatable from other parents. Retention policies, where children are forcibly kept in hospital until their hospital bill was paid may also have been influential in the decision-making process (Mostert et al., 2014).

Without making any assumptions about any of the countries or hospitals in this review, clinicians and others should pay attention to the wider structure in which healthcare is delivered, as poorly focussed funding may not improve the situation or even exacerbate it if it is wasted on inappropriate interventions (such as equipment in the absence of skilled operators) or if it feeds corrupt practices. Thus attention needs to be paid at all levels: governmental, hospital, healthcare provider and individual patient level intervention (Mostert et al., 2015). Explicit paediatric cancer strategies and funding may be important to prioritise and focus these aspects of care (Weaver et al., 2015a).

The quality of the evidence supporting this conclusion as defined by GRADE is the extent to which one can be confident that an estimate of effect or association is close to the quantity of specific interest (Schünemann et al., 2013). The within-study risk of bias using the Newcastle Ottawa scale was good for all categories apart from outcome, where most studies had a large loss of subjects which had an unknown effect on the results. The directness of

evidence to any one country was limited due to the small number of countries from which the studies originated, with the largest number coming from Kenya.

Although a meta-analysis was undertaken for some predictors there were too few studies to assess heterogeneity or to come to any conclusion about the precision of the risks or proportions. There is also little evidence on which to base an assessment of publication bias, apart from noting the relative paucity of literature in this area. An additional source of heterogeneity was introduced by the different cancers, which have very different treatment regimes in terms of duration, supportive care, chemotherapy, surgery, radiotherapy and late-effects (Gelband et al., 2015); however all place significant burdens on health systems and families and a major advance would be if regimens could be simplified.

In order to inform treatment more robust research is needed to identify the extent of this problem, and how it differs according to geographical region, as well as by disease and patient characteristics. There is also a great need to have a better understanding of this phenomenon from the perspective of the patients and their families, as this review has shown that in many cases the reasons for treatment abandonment are not known. This may also be related to parental health literacy as there is additional evidence from other areas, such as mental health, that how illness is understood in Sub-Saharan Africa may differ markedly from the accepted medical view (Atelola, 2015), a finding reflected in some of these studies. Only when these are understood can interventions be implemented and evaluated.

This phenomenon of not completing treatment is not just one of concern in cancer care; similar problems are seen in other conditions which require long-term treatment such as tuberculosis and HIV. In the case of TB it is particularly challenging, as there are broader

public health concerns about the development of resistance in those who are partially treated; while for HIV the treatment is life-long. Although the nature of these treatments and the context in which they are given differ making solutions difficult to transfer from one setting to another (Weaver et al., 2015b), what may be common to them is a need for research to go beyond finding treatments that can work in clinical studies (efficacy) to those that do work in practice for all children (effectiveness) and which are sustainable.

CONCLUSION

Based on these findings it would seem clear that more information is needed about the extent of treatment abandonment and the reasons for it, both from a medical perspective such as might be found in records or a cancer registry, but also from a parental perspective. However for any of this to make sense better diagnostic facilities and high quality population-based cancer registries are required. Additionally, healthcare professionals should inform parents of patients without insurance to enrol onto the relevant insurance programme in their location straight after diagnosis is confirmed, to help alleviate financial programmes; provide housing for patients and families close to the treatment centres, and develop community healthcare team that would be able to provide treatment at home or in a regional treatment closer than the larger treatment centres, and provide education surrounding the diagnosis and the importance of treatment compliance to help outcomes.

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PRISMA 2009 Flow Diagram

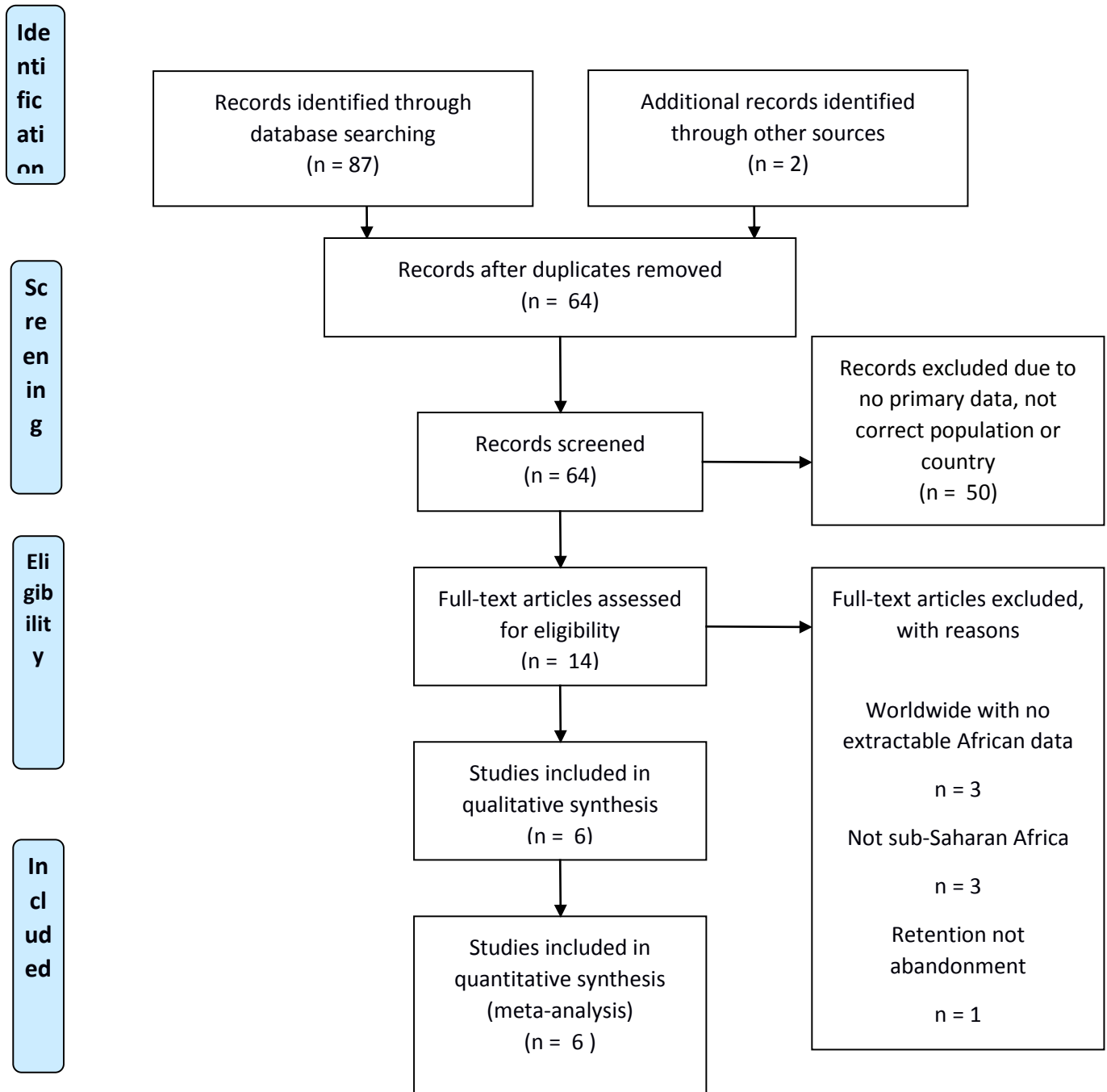
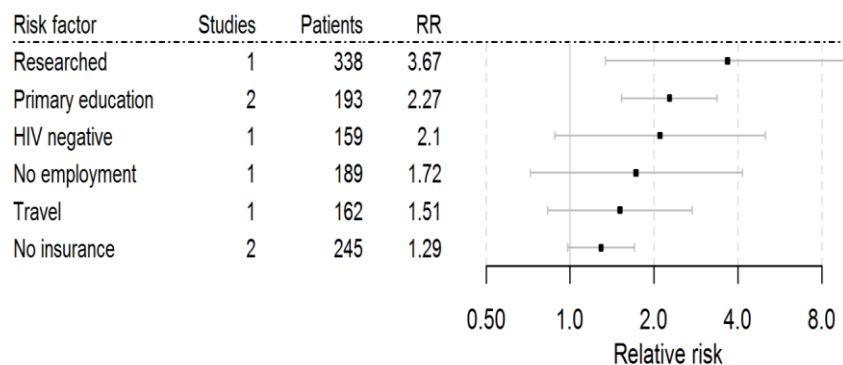
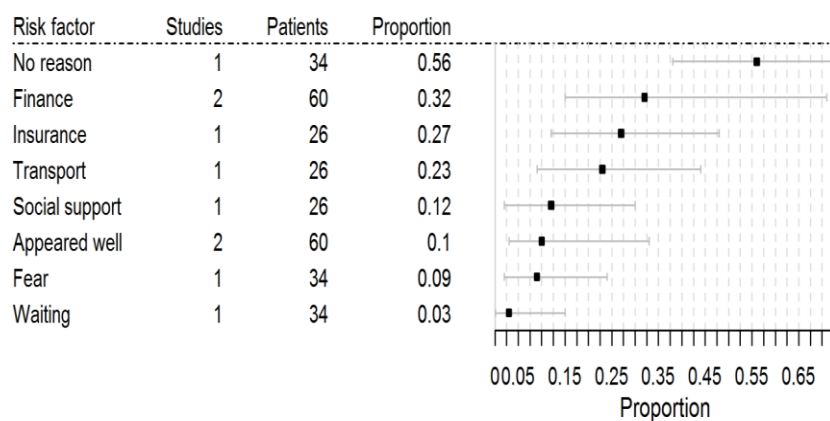


Figure 1: Study Selection

Factors associated with treatment abandonment



Reason for abandoning treatment



Study	Country and study type	Selection	Comparability	Outcome
Axt (2013)	Multi-centre cohort, Kenya	****	**	** (-1 due to loss of subjects)
Libes et al (2015)	Multi-centre cohort, Kenya	****	* (-1 no control)	** (self-report but this is appropriate, -1 due to loss of subjects)
Mostert et al (2014)	Single-centre cohort, Kenya	****	**	** (-1 due to loss of subjects)
Mtete et al (2016)	Single-centre cohort, Lalawi	***(-1 due to different cancers)	* (-1 due to different cancers)	** (-1 due to loss of subjects)
Njuguna et al (2014)	Single-centre cohort, Kenya	****	* (-1 no control)	** (self-report but this is appropriate, -1 due to loss of subjects)
Sloane et al (2014)	Single-centre cohort, Zambia	****	**	** (-1 due to loss of subjects)

Table 1: Summary of Findings using the Newcastle-Ottawa Scale